

REMARKS

Claims

Claims 1 and 5 are currently amended; claims 2-4 and 10-11 are cancelled.

Claim 1 is herein amended to incorporate a chemical structure consistent with that of Figure 1 for reasons of clarity, as suggested by the Examiner. Claim 1 now has the alkyl group R of the alkyl ether group OR including any of a saturated, unsaturated or cycloalkyl. Support for these amendments in claims 1 are found in the application on p. 2, lines 15-16 ("Moreover the alkyl ether functional group can include any of a long chain saturated alkyl, a long chain unsaturated alkyl, or a cycloalkyl group") and Figure 1.

Claim 5 is amended to add back the word "according" before the phrase "to claim 1" which was inadvertently deleted in Response B, filed August 11, 2003. Applicants respectfully submit that no new matter is added with these amendments.

Rejection Under 35 USC § 103(a)

Applicants respectfully submit that the pending claims are patentable over Simpkins et al. (US 5,554,601) because, as presented in detail in Response B filed August 11, 2003, there is no suggestion in Simpkins et al. (the '601 patent), or the knowledge generally available in the art, to particularly use an alkyl ether chain, including a long chain saturated alkyl, a long chain unsaturated alkyl, or a cycloalkyl as the alkyl group in the alkyl ether group, at position 17 of the D ring of the estrogen compounds in Simpkins et al., (the R₂ group in Simpkins et al.). Although many possible R₂ groups are presented in Simpkins et al., there is no particularity indicated in the possibility for R₂ groups in the '601 patent, no suggestion in the '601 patent or the knowledge generally available in the

art, that long chain alkyl ethers of the type claimed in the instant application are especially desirable for providing cytoprotection of cells.

The Examiner alleges that in col. 11-54 of col. 3 and lines 1-42 of col. 4 in the examples depicted, and especially in claim 4, that the '601 patent discloses and claims 17-substituted estra-alkyl ethers. The Examiner then alleges that the formula in col. 4 and the lists of R groups in Figs. 9A and 9B show valerate, stearate and benzyl ether as examples and although methyl ether and ethyl ether steroids are disclaimed in the instant application, the others are still obvious.

Applicants would like to point out that the only ether substituents disclosed in the '601 patent at the 17 position of the steroid core compound are ethyl ether, benzyl ether, and the glucuronides (sugar acids). As Dr. Simpkins states in his declaration (hereinafter "Declaration"), "there are a number of typographical errors in the chemical structures listed for the various R₁ and R₂ substituents in Figure 9A of issued U.S. Patent No. 5,554,601. In fact, the typographical errors in the '601 patent may have contributed to its being cited (erroneously, in my opinion,) as a 103(a) reference against the instant application." See Declaration, para. 4. Dr. Simpkins goes on to explain that "In particular, methyl ester, valerate, stearate, and enanthate are missing the subscript 2 after the oxygen in the structural formulas, and all are ester substituents, not ether substituents. In fact, the only ether substituents shown in Figure 9A are ethyl ether, benzyl ether, and the two glucuronides. None of the ethers disclosed in the '601 patent are long chain alkyl ethers. The compounds of the '601 patent are very different from the compounds claimed in the instant application." *Id.*

In light of the '601 patent disclosing mostly ester compounds and other variable substituents that are not ethers, Applicants respectfully submit that it is not obvious to modify the hydroxyl, methyl, ester, ketal, ethynyl- α , sugar acid, ketone, mineral acid, or tertiary amine substituents in the '601 patent, connected by a variety of linkages, with the long chain alkyl ether substituents in the instant application, connected only by C-O bonds. For the convenience of the Examiner, a copy of the Certificate of Correction, including the amended Fig.9A, is attached herewith (hereinafter "Amended Fig. 9A")

In addition, the instant application does not merely disclaim certain ether compounds, as implied by the Examiner in the Office Action, the instant application claims a series of estrogen compounds having a related series of alkyl ether substituents at the 17 position. These particular substituents are the subject of the instant application because it was surprisingly found that these exemplary embodiments of estrogens can exhibit 10-fold greater cytoprotection in a variety of cells, not just neuronal cells, relative to the core estrogenic compound from which the particular modified estrogen was derived, as long as the modified estrogen obeys the claimed limitations – i.e. there is an alkyl ether at carbon 17 of the D ring which is either a long chain saturated alkyl, long chain unsaturated alkyl, or cycloalkyl ether group. Further, it was surprisingly found that substituting with either too large a functional group or too small a functional group at the 17 position of the estrogen (R_2 in the 601 patent) can dramatically affect the cytoprotection capability of such modified estrogen compounds. See application, p. 16, line 14-p. 17, line 12. None of these insights are disclosed in the cited '601 patent reference.

As detailed previously in Response B, filed August 11, 2003, the R₂ substituents at the 17 position in the compounds disclosed in the '601 patent are not related by any common chemical, electronic, or structural theme. They encompass substituents that are small or large, straight-chained or branched, aromatic or not, in the form of acids or salts, and linked through C-C, ether, ester, glycosidic, keto, or amino bonds. As shown in Figure 9A, the '601 patent provides a variety of possible substituents at the R₂ position, from -OH to benzoate, from ethynyl - α to ketal, from triethyl ammonium salt to sodium phosphate to (see Amended Fig. 9A, and Simpkins et al., claims 4-5 and 22, among others). Some of the possible R₂ groups in the '601 patent are esters, others are salts, some are hydroxyls, some are aromatic, some are branched, some are linear, some are short chains, some are long. There is no particularity for the R₂ substituents disclosed in the '601 patent, and no suggestion in the '601 patent, or the knowledge generally available in the art, that long chain alkyl ethers or cycloalkyl ethers are particularly desirable for providing cytoprotection in cells. As stated by Dr. Simpkins, "the particular substituents claimed in the instant application were chosen because they were unexpectedly found to exhibit 10-fold greater cytoprotection in general relative to other substituents investigated. ... selection of alkyl ether groups ... occurred because of unexpected and surprising research results that were obtained with compounds having substitutions at the 17 position with substituents that fell into this category of compounds. Such results were not observed with other estrogen compounds having other substitutions at the 17 position, including the compounds disclosed in the '601 patent." Declaration, para. 5.

In short, just because the '601 patent discloses substitution at the 17 position of the D ring of a steroid does not mean that all other substituents at the same position are rendered obvious. There must be some suggestion or motivation to modify in the reference itself or the knowledge generally available, not just to modify *in general*, but to modify *specifically*, to arrive at the compounds claimed in the instant application.

Applicants again respectfully submit that such a suggestion, in the reference or the knowledge generally available, is not present and that the Examiner has not provided *prima facie* evidence that it is. In fact, Dr. Simpkins himself states that "the unexpected and surprising cytoprotective characteristics of the compounds claimed in the instant application were not suggested and were not obvious given the knowledge of the compounds in the '601 patent, or given the knowledge generally available in the field."

Declaration, para. 6.

Applicants would also like to point out that the comment in the Office Action that "US '601 teaches that "estrogen compound" is defined as any structure described in the 11th edition of "steroids" from Steraloids, Inc." and is the same reference and same definition as in the instant application, and that both the '601 patent and the instant application incorporate this reference, does not speak to the issue of obviousness. Both applications have chosen to use the same reference to define what is meant by the term "estrogen." But using the same reference to define a very broad class of chemical compounds in no way signifies that all estrogen compounds within that definition for steroids are therefore obvious.

In summary, claims 1 and 5-9 of the instant application require an alkyl ether substituent on carbon 17 of the D ring, wherein the alkyl group is either a long-chain

saturated alkyl group, a long-chain unsaturated alkyl group, or a cycloalkyl group. Nothing in the '601 patent discloses that the R₂ position could be, or more importantly, should be, a long-chain alkyl ether, whether saturated, unsaturated, or a cycloalkyl ether. As stated above, the claimed estrogen compounds having the disclosed particular substituents at position 17 of the D ring have been found to convey surprisingly increased cytoprotection, in general, on a wide-variety of cells relative to the generic estrogen compounds disclosed in the '601 patent having non-particular substituents at position 17 of the D ring, which are disclosed to confer cytoprotection only to neuronal cells. See p. 17, lines 3-13 of the present application, which describes that this discovery was unexpected and led to the present definition of n to be at least 3 and less than 20. This element of the present claims was an unexpected and nonobvious discovery over the disclosure of the '601 patent. For these reasons, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness and that the claims are patentable over Simpkins '601. Reconsideration and withdrawal of the obviousness rejection under §103(a) is therefore requested.

Rejection under 35 USC § 112, para. 1 (written description/new matter)

Although the Examiner alleges on p. 4 of the Office Action of November 12, 2003 that there is no support for the phrase "a long chain unsaturated alkyl" in claim 1, Applicants respectfully draw the Examiner's attention to p. 2, lines 15-16, of the specification, and to original claim 1 and to original claim 6 (and as previously pointed out in Response B filed August 11, 2003) and herein re-submit that no new matter has been added by this amendment. Further, a telephone conversation with Supervisory Primary

Examiner Thurman Page on March 31, 2004 resulted in an agreement by Examiner Page, for the record, that the new matter rejection relating to this subject matter that was asserted in the Office Action of November 12, 2003 on p. 4, section 8, will not be maintained. Reconsideration and withdrawal of the rejection under 35 USC § 112, para. 1 (new matter), is therefore requested.

Request for complete reference to Gridley et al. referred to on p. 1 of the Specification

Applicant apologizes for the incomplete reference, and herein provides the requested information:

Gridley K.E., Green, P.S., and Simpkins, J.W., *Mol. Pharmacol.* (1998) Nov; 54(5):874-880. A novel, synergistic interaction between 17 beta-estradiol and glutathione in the protection of neurons against beta-amyloid 25-35-induced toxicity *in vitro*.

Department of Pharmacodynamics and Center for Neurobiology of Aging, College of Pharmacy, University of Florida, Gainesville, Florida 32610, USA.

The present studies were undertaken to investigate the possibility of an interaction between 17 beta-estradiol (E2) and glutathione in protecting cells against the presence of beta-amyloid 25-35 (β -AP 25-35). We demonstrate that when evaluated individually, supraphysiological concentrations of either E2 (200 nM) or of reduced glutathione (GSH; 325 μ M) can protect SK-N-SH human neuroblastoma cells from β -AP 25-35 (20 μ M) toxicity. This dose of β -AP 25-35 was chosen based on the LD50 (28.9 μ M) obtained in our earlier work. However, in the presence of 3.25 μ M GSH, the neuroprotective EC50 of E2 was shifted from 126 ± 89 nM to 0.033 ± 0.031 nM, approximately 4000-fold. Similarly, in primary rat cortical neurons, the addition of GSH (3.25 μ M) increased the potency of E2 against β -AP 25-35 (10 μ M) toxicity, as evidenced by a shift in the EC50 values of E2 from 68 ± 79 nM in the absence of GSH to 4 ± 6 nM in its presence. The synergy between E2 and GSH was not antagonized by the addition of the estrogen receptor antagonist, ICI 182,780. Other thiol-containing compounds did not interact synergistically with E2, nor were any synergistic interactions observed between E2 and ascorbic

acid or alpha-tocopherol. Based on these data, we propose an estrogen-receptor independent synergistic interaction between glutathione and E2 that dramatically increases the neuroprotective potency of the steroid and may provide insight for the development of new treatment strategies for neurodegenerative diseases.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all pending claims are in condition for allowance. Reconsideration of the claims and a notice of allowance are therefore requested.

Applicant submits herewith a Petition for a two-month extension of time, along with the requisite fees. Applicants believe that no additional fees are required. If, however, additional fees are required for the timely consideration of this response, Applicants authorize the Commissioner to charge deposit account number 19-4972 for any additional fees that may be required for the timely consideration of this application.

Date: April 12, 2004

Respectfully submitted,


Barbara J. Carter, Ph.D.
Registration No. 52,703
Attorney for Applicants

Bromberg & Sunstein LLP
125 Summer Street
Boston, Massachusetts 02110-1618
Tel: (617) 443-9292
Fax: (617) 443-0004



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Prokai et al. Art Unit: 1616
Appl. No: 09/893,324 Examiner: Sabiha N. Qazi
Filing Date: June 27, 2001 Docket No.: 1540/139
Invention: ALKYL ETHER MODIFIED POLYCYCLIC COMPOUNDS HAVING A
TERMINAL PHENOL AND USES FOR PROTECTION OF CELLS

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Commissioner for Patents, Box 1450, Alexandria, VA, 22313-1450 on April 12, 2004.

Barbara J. Carter
Barbara J. Carter

Honorable Commissioner of Patents
Alexandria, VA 22313-1450

**DECLARATION OF JAMES W. SIMPKINS, PH.D., (APPENDIX A)
IN SUPPORT OF APPLICANTS' RESPONSE
[37 C.F.R. § 1.132]**

Dear Sir:

In response to the Office Action mailed November 12, 2003, in the above-referenced matter, I hereby declare as follows:

1. My name is James W. Simpkins, Ph.D. I am one of the inventors of the subject matter of the above patent application and am an inventor on a number of other patents and pending patent applications involving estrogens in the therapy of Alzheimer's disease, stroke and other neurodegenerative conditions, including U.S. Patent No. 5,554,601, currently cited in the present office action (the '601 patent). I am also an author or co-author of a number of publications involving estrogen compounds, including (Dykens, J.A., **J.W. Simpkins**, J. Wang and K. Gordon. Polyphenolic Steroids and Neuroprotection: A proposed mitochondrial mechanism. *Experimental Gerontology*, 38:

101-107, 2003; Wang, X., J.W. Simpkins, J.A. Dykens and P.R. Cammarata. Effects of estrogens against oxidative damage to human lens epithelial cells in culture. Part 1: Protection of mitochondria; potential, intracellular ATP and cell viability. *Investigative Ophthalmology & Visual Science*, 44: 2067-2075, 2003; Aoun, P., J.W. Simpkins, N. Agarwal. PPAR- γ ligands are neuroprotective against glutamate induced cytotoxicity in retinal ganglion cells. *Investigative Ophthalmology & Visual Science*, 44:2999-3004, 2003; Kaja, S., S.H. Yang, J. Wei, K. Fujitani, R. Liu, A.M. Brun-Zingernagel, J.W. Simpkins, K. Inokuchi and P. Koulen. Estrogen protects the inner retina from apoptosis and ischemia-induced loss of Vesl-1L/Homer 1c immunoreactive synaptic connections. *Investigative Ophthalmology & Visual Science*, 44: 3155-3162, 2003; Aoun, P. and J.W. Simpkins. Neuroprotective effects of PPAR- γ agonists against oxidative insults in HT-22 cells. *European J. Pharmacology*, 472: 65-71, 2003; L. Prokai, K. Prokai-Tatrai, P. Perjesi, A. Zharikova and J.W. Simpkins. Quinol-based bioreversible metabolic cycle for estrogens in rat liver microsomes. *Drug Metabolism and Disposition*, 31: 701-704, 2003; and L. Prokai, K. Prokai-Tatrai, P. Perjesi, A. Zharikova, E. Perez, R. Liu and J. Simpkins, Quinol-based cyclic antioxidant mechanism in estrogen neuroprotection. *Proc. National Academy of Sciences USA* 100: 11741-11746, 2003) and I have a strong background in biology, pharmacology and neuroscience, determination of the role of estrogens in the therapy of Alzheimer's disease, stroke and other neurodegenerative conditions, and determination of the structure-activity relationship of steroids in neuroprotection.

2. I received a Ph.D. Degree in Physiology from Michigan State University and joined the faculty at the University of Florida, College of Pharmacy in 1997 and

advanced to Professor of Pharmacodynamics. I have served as Chairman of the Department of Pharmacodynamics, Chairman of the Department of Pharmaceutics, Associate Dean for Research and Graduate Studies and Director, Center for the Neurobiology of Aging at the University of Florida. In 1996, I was appointed as the Frank Duckworth Professor of Drug Discovery at the University of Florida. I have more than 250 peer-reviewed publications, a dozen patents and have edited two texts on Alzheimer's disease therapy. I have also served as the Director of the University of Florida Drug Discovery Group for Alzheimer's disease, which has sustained funding by the National Institute on Aging to support research in the pharmacotherapy for Alzheimer's disease. In 1999 I was appointed to the Medical and Scientific Advisory Council of the National Alzheimer's Association.

3. In July of 2000, I became the Chair of the Department of Pharmacology and Neuroscience and Director, Institute for Aging and Alzheimer's Disease Research at the University of North Texas Health Science at Fort Worth. My further credentials are set forth in an abbreviated Curriculum Vita, which is attached hereto as Appendix B.

4. I have read the action of November 12, 2003. This declaration is provided to state for the record that the claimed subject matter in the instant application (serial no. 09/893,324) is not obvious in light of issued U.S. Patent No. 5,554,601 to Simpkins et al., as well as to state for the record that there are a number of typographical errors in the chemical structures listed for the various R₁ and R₂ substituents in Figure 9A of issued U.S. Patent No. 5,554,601. In fact, the typographical errors in the '601 patent may have contributed to its being cited (erroneously, in my opinion,) as a 103(a) reference against the instant application. Thus, a certificate of correction has been filed to address these

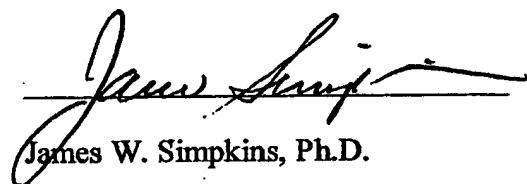
errors. In particular, methyl ester, valerate, stearate, and enanthate are missing the subscript 2 after the oxygen in the structural formulas, and all are ester substituents, not ether substituents. In fact, the only ether substituents shown in Figure 9A are ethyl ether, benzyl ether, and the two glucuronides. None of the ethers disclosed in the '601 patent are long chain alkyl ethers. The compounds of the '601 patent are very different from the compounds claimed in the instant application.

5. The '601 patent does not disclose substituents for the 17 position of the core estrogen compound that fall within the required limitations of the substituents claimed in the instant application. Further, the particular substituents claimed in the instant application were chosen because they were unexpectedly found to exhibit 10-fold greater cytoprotection in general relative to other substituents investigated. The particular substituents of the instant application did not arise as a natural progression from the experiments disclosed in the '601 patent, nor did the disclosure of the '601 patent suggest these particular substituents. Rather, selection of alkyl ether groups wherein the alkyl group of the alkyl ether includes long chain saturated alkyl, long chain unsaturated alkyl, or long chain cycloalkyl groups occurred because of unexpected and surprising research results that were obtained with compounds having substitutions at the 17 position with substituents that fell into this category of compounds. Such results were not observed with other estrogen compounds having other substitutions at the 17 position, including the compounds disclosed in the '601 patent.

6. In summary, the unexpected and surprising cytoprotective characteristics of the compounds claimed in the instant application were not suggested and were not obvious given the knowledge of the compounds in the '601 patent, or given the knowledge

generally available in the field. Please consider these comments in conjunction with the response submitted herewith.

7. I hereby declare that all statements made herein are of my own knowledge and that all statements made on information and belief are true; and further that these statements are being made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



James W. Simpkins, Ph.D.

Dated: April 12, 2004

Appendix B

James Simpkins , Ph.D.

Professor and Department Chair

Department: Pharmacology & Neuroscience

Office: UNTHSC

Phone: 817-735-0498

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Faculty URL: neuropharm.hsc.unt.edu/Aging/Simpkins/main.htm

Biographical Sketch

Assessment of the potency, efficacy and mechanisms of action for the neuroprotective effects of estratrienes, of which 17 beta-estradiol is a member. Determination of the role of estrogens in the therapy of Alzheimer's disease, stroke and other neurodegenerative conditions. Determination of the structure-activity relationship of steroids in neuroprotection. Determination of the uses of estrogens in the treatment of non-neuronal disease that have a cytodegenerative component.

Education

University of Toledo 1971 B.S. Biology

University of Toledo 1974 M.S. Biology

Michigan State University 1977 Ph.D. Physiology

Representative Publications

1. Dykens, J.A., **J.W. Simpkins**, J. Wang and K. Gordon. Polyphenolic Steroids and Neuroprotection: A proposed mitochondrial mechanism. *Experimental Gerontology*, 38: 101-107, 2003.
2. Wang, X., **J.W. Simpkins**, J.A. Dykens and P.R. Cammarata. Effects of estrogens against oxidative damage to human lens epithelial cells in culture. Part 1: Protection of mitochondria; potential, intracellular ATP and cell viability. *Investigative Ophthalmology & Visual Science*, 44: 2067-2075, 2003.
3. Aoun, P., **J.W. Simpkins**, N. Agarwal. PPAR- γ ligands are neuroprotective against glutamate induced cytotoxicity in retinal ganglion cells. *Investigative Ophthalmology & Visual Science*, 44:2999-3004, 2003.
4. Kaja, S., S.H. Yang, J. Wei, K. Fujitani, R. Liu, A.M. Brun-Zingernagel, **J.W. Simpkins**, K. Inokuchi and P. Koulen. Estrogen protects the inner retina from apoptosis and ischemia-induced loss of Vesl-1L/Homer 1c immunoreactive synaptic connections. *Investigative Ophthalmology & Visual Science*, 44: 3155-3162, 2003.
5. Aoun, P. and **J.W. Simpkins**. Neuroprotective effects of PPAR- γ agonists against oxidative insults in HT-22 cells. *European J. Pharmacology*, 472:

65-71, 2003.

6. L. Prokai, K. Prokai-Tatrai, P. Perjesi, A. Zharikova and **J.W. Simpkins**, Quinol-based bioreversible metabolic cycle for estrogens in rat liver microsomes. *Drug Metabolism and Disposition*, 31: 701-704, 2003.
7. L. Prokai, K. Prokai-Tatrai, P. Perjesi, A. Zharikova, E. Perez, R. Liu and **J. W. Simpkins**, Quinol-based cyclic antioxidant mechanism in estrogen neuroprotection. *Proc. National Academy of Sciences USA* 100: 11741-11746, 2003.
8. Rewal, M., M. E. Jung, Y. Wen, A.-M. Brun-Zinkernagel and **J. W. Simpkins**, Role of the GABA-A System in behavioral, motoric and cerebellar protection by estrogen during ethanol withdrawal, *Alcohol* 31: 49-61, 2003.
9. Jung, M. E., D. G. Watson, Y. Wen and **J. W. Simpkins**, Role of protein kinase C in estrogen protection against apoptotic cerebellar cell death in ethanol withdrawn rats, *Alcohol* 31: 39-48, 2003.
10. Fan, T. S.H. Yang, E. Johnson, B. Osteen, R. Hayes, A. L. Day and **J. W. Simpkins**, 17 β -estradiol can extend ischemic thresholds and exert neuroprotective effects in cerebral subcortex against transient focal ischemia in rats, *Brain Research* 993: 10-17, 2003.

Funding

Discovery of Novel Drugs for Alzheimer's Disease, NIH P01 AG10485
Neuroprotective Effects of Estrogens and Related Steroids, Apollo Genetics, Inc.
Neuroprotection from Brain Injury by Novel Estrogens, U.S. Army
Training in the Neurobiology of Aging, NIH AG00196

Memberships

Endocrine Society
American Physiological Society
Sigma Xi
American Association for the Advancement of Science
Society for Neuroscience
The Gerontological Society
American Association of Pharmaceutical Scientists
Society for the Study of Ingestive Behavior
American Association of Colleges of Pharmacy
Southeastern Pharmacological Society

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Number: 5,554,601
Issued: September 10, 1996
Name of Patentee: University of Florida Research Foundation, Inc.
Title of Invention: Methods for Neuroprotection

COPY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**REQUEST FOR CERTIFICATE OF CORRECTION OF PATENT
FOR APPLICANT'S MISTAKE (37 C.F.R. section 1.323)**

1. It is noted that an error appears in this patent of a minor nature or character, as more fully described below. It occurred in good faith. Correction thereof does not involve such changes in the patent as would constitute new matter or would require re-examination. A certificate of correction is requested.
2. Attached hereto, in duplicate, is Form PTO-1050, with at least one copy being suitable for printing.
3. The exact page and line number where the error occurs in the application file are:

Figure 9A of application.

4. Please send the Certificate to:

Barbara J. Carter
BROMBERG & SUNSTEIN LLP
125 Summer Street
Boston, MA 02110-1618
US

5. Please pay the fee required by 37 C.F.R. § 1.20(a), as follows:

Authorization is hereby made to charge the amount of \$100.00 to Deposit Account No. 19-4972.

Charge any additional fees required by this paper or credit any overpayment in the manner authorized above.

A duplicate of this paper is attached.

Date: April 12, 2004

Barbara J. Carter

Barbara J. Carter
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Boston, MA 02110-1618
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617-443-9292
Customer No. 02101

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO : 5,554,601

DATED : September 10, 1996

INVENTOR(S) : Simpkins et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Figure 9A (see attached)

MAILING ADDRESS OF SENDER:

Barbara J. Carter
Bromberg & Sunstein LLP
125 Summer Street
Boston, MA 02110-1618

PATENT NO. 5,554,601

No. of additional copies

→ 10

This collection of information is required by 37 CFR 1.322, 1.323, and 1.324. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1.0 hour to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Attention Certificate of Corrections Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

R ₁ AND/OR R ₂ SUBSTITUTIONS	
NAME	STRUCTURE
HYDROXYL	$\xi\text{-OH}$
METHYL	$\xi\text{-CH}_3$
METHYL ESTER (FORMATE)	$\xi\text{-O-C(=O)H}$
ACETATE	$\xi\text{-O-C(=O)CH}_3$
ETHYL ETHER	$\xi\text{-O-CH}_2\text{-CH}_3$
3,3 (OR 17,17) DIMETHYL KETAL	$\begin{array}{c} \xi \\ \\ \text{OCH}_3 \\ \\ \text{OCH}_3 \\ \\ \text{C}\equiv\text{CH} \\ \\ \text{OH} \end{array}$
ETHYNYL- α	$\begin{array}{c} \xi \\ \\ \text{C}\equiv\text{CH} \\ \\ \text{OH} \end{array}$
BENZOATE	$\xi\text{-O-C(=O)}\text{C}_6\text{H}_5$
BENZYL ETHER	$\xi\text{-O-CH}_2\text{C}_6\text{H}_5$
GLUCURONIDE	$\begin{array}{c} \text{O} \\ \\ \text{C} \\ \\ \text{O} \\ \\ \text{C} \\ \\ \text{O} \\ \\ \text{C} \\ \\ \text{O} \end{array}$
SULFATE, SODIUM SALT	$\xi\text{-O-S(=O)(=O)O}^-\text{Na}^+$
OXIDE	$\begin{array}{c} \text{O} \\ \\ \text{O} \end{array}$
VALERATE	$\xi\text{-O-C(=O)}\text{(CH}_2\text{)}_3\text{CH}_3$
CYCLOPENTYLPROPIONATE (CYPIONATE)	$\xi\text{-O-C(=O)}\text{(CH}_2\text{)}_2\text{C}_5\text{H}_9$
PROPIONATE	$\xi\text{-O-C(=O)CH}_2\text{CH}_3$
HEMISUCCINATE	$\xi\text{-O-C(=O)}\text{(CH}_2\text{)}_2\text{-C(=O)OH}$

FIG.9A

BC:klw

Please Date Stamp and Return

The Commissioner for Patents has received from Bromberg & Sunstein LLP the following re:

Inventor: Prokai et al. Docket No.: 1540/139

Title: Alkyl Ether Modified Polycyclic Art Unit: 1616

Compounds Having a Terminal Examiner: Sabiha Naim Qazi

Phenol & Uses for the Protection

of Cells

Serial/Patent No.: 09/893,324 Date: April 12, 2004

Filing/Issue Date: June 27, 2001 Express Mail No.:

Documents:

- New Application Transmittal
- Provisional Application Cover Sheet
- Description- pages
- Claims- pages
- Abstract
- Application Data Sheet
- Request and Certification under 35 USC 122(b)(2)(B)(i) sheets of drawings
- formal informal
- Declaration & Power of Attorney
- excused unexecuted
- Appendix A Declaration by James W. Simpkins
- Appendix B Curriculum Vitae of James W. Simpkins
- Assignment/Recordation Form Cover Sheet
- Check in the amount of \$
- Completion of Filing Requirements
- Transmittal of Formal Drawings
- Copy of Request for Certificate of Correction for Patent No. 5,554,601 (1540/105)

BROMBERG & SUNSTEIN LLP

125 SUMMER STREET BOSTON MA 02110-6118

15401139

Commissioner for Patents
P.O. Box 1450
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